REMARKS

This case was subject to a restriction requirement between Claims 1-5 and 6-9, as originally filed. Applicant elected Claims 6-9 for initial prosecution. Applicant has concurred with an initial action on Claims 6-9, that the claims do not recite patentable subject matter, as presently written. Accordingly, applicant is filing this divisional case to continue prosecution based on Claims 1-5.

In the office action on Claims 6-9, the Examiner comments that the applicant "wishes to claim crystals that they desire to make and not those that have been prepared in reality." This is incorrect. The entire process claimed by applicant is based on crystallography data obtained from an unknown crystal that is in existence, where the process enables an electron density map to be prepared for use in characterizing the crystal structure.

Claims 10-14 are presented for examination.

Respectfully submitted,

Date: Oct. 16, 2001

Signature of Attorney

Reg. No. 28,351
Phone (505) 665-3112

Ray G. Wilson
Los Alamos National Laboratory
LC/BPL, MS D412
Los Alamos, New Mexico 87545

ATTACHMENT A

SUMMARY OF THE INVENTION

In accordance with the purposes of the present invention, embodied and broadly described herein, the present invention includes a method for improving an electron density map of an experimental crystal structure. A model electron density map of a model crystal structure is formed and model histograms are formed of model electron densities in identified protein and solvent regions of the model electron density map. A model probability distribution function defined by

$$p(\rho_T) = \sum_k w_k \exp\left\{-\frac{(\rho - c_k)^2}{2\sigma_k^2}\right\}$$

is fitted to the model histograms, where k is separately indexed over the protein and solvent regions of the model map, $p(\rho_T)$ is a probability of an electron density at a point, w_k is a normalization factor, ρ is electron density, c_k is a mean value of ρ, and σ_k is a variance of ρ, where the fitting determines the coefficients w_k, c_k, and σ_k. A set of experimental structure factors is determined from x-ray diffraction data for the experimental crystal structure and forming an experimental electron density map and separate experimental histograms of experimental electron densities are formed over protein and solvent regions of the model electron density map. An experimental probability distribution function defined by

$$p(\rho_T) = \sum_k w_k \exp\left\{-\frac{(\rho - \beta c_k)^2}{2(\beta\sigma_k^2 + \sigma_{MAP}^2)}\right\}$$

is fitted to separate protein and solvent regions of the experimental histograms, where β is an expectation that an experimental value of ρ is less than a true value and σ_{map} is a variance, where the fitting determines the coefficients β and σ_{map}. From the experimental probability distribution function the overall experimental log-likelihood of the electron density in the protein and solvent regions of the experimental map is determined. Then, it is determined how the experimental log-likelihood of the electron density of the protein and solvent regions of the experimental electron density map

would change as each experimental structure factor changes to output a revised log-likelihood of any value of each experimental structure factor. Finally, a new set of structure factors is formed from the revised log-likelihood of experimental structure factor values and the new set of structure factors is returned iterate the process until changes to the new set of structure factors is below a predetermined value.

CLAIMS

10. A method for improving an electron density map of an experimental crystal structure, comprising the steps of:

a. forming a model electron density map of a model crystal structure;

b. forming model histograms of model electron densities in identified protein and solvent regions of the model electron density map;

c. fitting a model probability distribution function defined by

$$p(\rho_T) = \sum_k w_k \exp\left\{-\frac{(\rho - c_k)^2}{2\sigma_k^2}\right\}$$

to the model histograms, where k is separately indexed over the protein and solvent regions of the model map, $p(\rho_T)$ is a probability of an electron density at a point, w_k is a normalization factor, ρ is electron density, c_k is a mean value of ρ, and σ_k is a variance of ρ, where the fitting determines the coefficients w_k, c_k, and σ_k;

d. determining a set of experimental structure factors from x-ray diffraction data for the experimental crystal structure and forming an experimental electron density map;

e. forming separate experimental histograms of experimental electron densities over protein and solvent regions of the model electron density map;

f. fitting an experimental probability distribution function defined by

$$p(\rho_T) = \sum_k w_k \exp\left\{-\frac{(\rho - \beta c_k)^2}{2(\beta\sigma_k^2 + \sigma_{MAP}^2)}\right\}$$

to separate protein and solvent regions of the experimental histograms, where β is an expectation that an experimental value of ρ is less than a true value and σ_{map} is a variance, where the fitting determines the coefficients β and σ_{map};

g. determine from the experimental probability distribution function the overall experimental log-likelihood of the electron density in the protein and solvent regions of the experimental map;

h. determine how the experimental log-likelihood of the electron density of the protein and solvent regions of the experimental electron density map would change as each experimental structure factor changes to output a revised log-likelihood of any value of each experimental structure factor; and

i. forming from the revised log-likelihood of experimental structure factor values a new set of structure factors and returning the new set of structure factors to step (f) to iterate the process until changes to a new set of structure factors are below a predetermined value.

11. A method according to Claim 10, wherein step a. further includes a step of selecting the model crystal structure to be similar in size, data resolution, and atomic displacement factors to the experimental crystal structure.

12. A method according to Claim 10, wherein step b. further includes a step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points at "solvent."

13. A method according to Claim 11, wherein step b. further includes a step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points at "solvent."

14. A method according to Claim 10, wherein step h. includes steps of forming a Taylor's series expansion of the log-likelihood of the experimental electron density map and evaluating terms of the Taylor's series expansion using a Fast Fourier Transform.